Online Data Supplement–Title Page

Title: Renin-angiotensin-aldosterone System Inhibitors and Risks of SARS-CoV-2 Infection: A Systematic Review and Meta-analysis

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This supplementary appendix provides:

1. Methods and Search equation via PubMed, EMBASE, MEDLINE, and Cochrane library
2. Strength of the study
3. PRISMA checklist.
4. Summary of contextual factor data.
5. PROSPERO protocol registration.
6. Quality assessment of the GRADE results.
7. Flow chart showing Search strategy for studies in China.
8. Supplemental Tables and Figures: flow chart, meta-regression analysis, and subgroup analysis of the forest plot of odds ratio (OR) and 95% confidence interval (CI).

1. Methods and Search equation via PubMed, EMBASE, MEDLINE, and Cochrane library

The following search terms were used to identify relevant articles: (COVID-19 OR COVID OR novel coronavirus 2019 OR coronavirus disease 2019 OR 2019-nCoV OR SRAS-CoV-2) AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent). We did not limit our search by language and focused on publications of human subjects and case-population or cohort studies. A manual search of reference lists of review articles was performed to identify additional reports not found in the computerized databases.

Study Selection

The searched articles were first evaluated by two independent investigators (CKC and HWL) at the level of titles or abstracts for inclusion. If there were disagreements, the comments from a third reviewer (VCW) were sought. For potentially relevant searched articles, the full version was further retrieved and evaluated according to the selection criteria. In order to provide the highest quality of the meta-analysis, we especially focused on those published articles not only providing patients with positive SARS-CoV-2 test results and information on the use of RAASi, but also simultaneously providing negative control cases with negative SARS-CoV-2 test results and information on the use of RAASi. Such inclusion criteria and the numbers of studies included distinguishing our study from all the others. Eligible studies were case-control or cohort studies reporting on the risk factors of SRAS-CoV-2 infection, including with and without the use of RAASi, and the test results of SARS-CoV-2. When the results of a study were reported in multiple publications, the most informative and recent publication was included in the analysis. Articles that were duplicate publications, case reports, reviews, editorials, letters, and commentaries were excluded. The diagram of the literature search and selection is shown in (Supplemental Figure 1)

The results of aOR were considered as the primary analysis while those of cOR were considered as the secondary analysis.

Outcomes of Interests

The primary outcome was the positive SARS-CoV-2 infection. Secondary outcomes were the severe infection (including ventilator use or intensive care unit admission) or mortality of COVID-19. Crude odds ratio (cOR) and the 95% confidence interval (CI) were directly calculated when the two by two cross-table was provided in all of the included studies. In contrast, adjusted odds ratio (aOR) and the 95% CI was also extracted. The results of aOR were considered as the primary analysis while those of cOR were considered as the secondary analysis.

Statistical Analysis

The pooled aOR for binary outcomes (i.e.: SARS-CoV-2 infection) was calculated in this meta-analysis. The data from individual studies were pooled using the DerSimonian and Laird (DL) random effect model. Inconsistency across studies was assessed using the I^2 statistics in which a value greater than 50% indicated a substantial heterogeneity. Furthermore, we performed a subgroup analysis according to the mean or median age of the study dichotomized by 60 years using a mixed effect model. Moreover, univariate random effect meta-regression was conducted to evaluate the possible effect modification of baseline characteristics, including the continuous age and the proportions of male gender, hypertension, diabetes mellitus, heart failure, and chronic kidney disease. Publication bias was detected by a funnel plot and an Egger's test. A sensitivity analysis that evaluated the impact of individual studies was performed by excluding each study one at a time, and the pooled odds ratio was re-estimated. The quantitative meta-analysis was conducted using Comprehensive Meta-Analysis version 3.3.070 (Biostat, USA).

Appendix.

Search strategies for the different databases ran on Jun 1, 2020.

PubMed Search Query

#1 ((2020/1/1:2020/6/1[Date - Publication] AND "English"[Language]) AND ((((((((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute

respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) OR "COVID"[All Fields] OR (((("novel"[All Fields] OR "novel s"[All Fields]) OR "novels"[All Fields]) AND (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]) AND "2019"[All Fields])) OR (("covid 19"[Supplementary Concept] OR "covid 19"[All Fields]) OR "coronavirus disease 2019"[All Fields])) OR (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields])) OR "SRAS-CoV-2"[All Fields])) AND ((((((((((("angiotensin converting enzyme inhibitors"[Pharmacological Action] OR "angiotensin-converting enzyme inhibitors"[MeSH Terms]) OR (("angiotensin converting"[All Fields] AND "enzyme"[All Fields]) AND "inhibitors"[All Fields])) OR "angiotensin converting enzyme inhibitors"[All Fields]) OR ((("angiotensin"[All Fields] AND "converting"[All Fields]) AND "enzyme"[All Fields]) AND "inhibitors"[All Fields])) OR "angiotensin converting enzyme inhibitors"[All Fields]) OR (((((("angiotensin receptor antagonists"[Pharmacological Action] OR "angiotensin receptor antagonists"[MeSH Terms]) OR (("angiotensin"[All Fields] AND "receptor"[All Fields]) AND "antagonists"[All Fields])) OR "angiotensin receptor antagonists"[All Fields]) OR (("angiotensin"[All Fields] AND "receptor"[All Fields]) AND "blockers"[All Fields])) OR "angiotensin receptor blockers"[All Fields])) OR "ACEi"[All Fields]) OR "ARBs"[All Fields]) OR (((((("renin-angiotensin system"[MeSH Terms] OR ("renin angiotensin"[All Fields] AND "system"[All Fields])) OR "renin angiotensin system"[All Fields]) OR (("renin"[All Fields] AND "angiotensin"[All Fields]) AND "system"[All Fields])) OR "renin angiotensin system"[All Fields]) AND (((((("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "inhibitors"[All Fields]) OR "inhibitor"[All Fields]) OR "inhibitor s"[All Fields]))) OR (((((("renin-angiotensin system"[MeSH Terms] OR ("renin angiotensin"[All Fields] AND "system"[All Fields])) OR "renin angiotensin system"[All Fields]) OR (("renin"[All Fields] AND "angiotensin"[All Fields]) AND "system"[All Fields])) OR "renin angiotensin system"[All Fields]) AND (("blocker"[All Fields] OR "blocker s"[All Fields]) OR "blockers"[All Fields]))) OR ("RAAS"[All Fields] AND (((((("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "inhibitors"[All Fields]) OR "inhibitor"[All Fields]) OR "inhibitor s"[All Fields]))) OR (((((("hypertense"[All Fields] OR "hypertension"[MeSH Terms]) OR "hypertension"[All Fields]) OR "hypertension s"[All Fields]) OR "hypertensions"[All Fields]) OR "hypertensive"[All Fields]) OR "hypertensive s"[All Fields]) OR "hypertensives"[All Fields])) OR (((((("antihypertensive agents"[Pharmacological Action] OR "antihypertensive agents"[MeSH Terms]) OR ("antihypertensive"[All Fields] AND "agents"[All Fields])) OR "antihypertensive agents"[All Fields]) OR ("antihypertensive"[All Fields] AND "agent"[All Fields])) OR "antihypertensive agent"[All Fields])) (556)

EMBASE

No. Query Results (728)

#1. ('covid 19'/exp OR 'covid 19' OR 'sars-cov-2'/exp OR 'sars-cov-2' OR 'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR '2019-ncov'/exp OR '2019-ncov') AND ('renin angiotensin aldosterone system blocker'/exp OR 'renin angiotensin aldosterone system blocker' OR 'angiotensin'/exp OR 'angiotensin' OR 'angiotensin receptor antagonist'/exp OR 'angiotensin receptor antagonist' OR 'hypertension'/exp OR 'hypertension' OR 'arb' OR 'acei') AND [humans]/lim AND [embase]/lim AND [1-1-2020]/sd NOT [2-6-2020]/sd

Medline (EBSCO) Search Query

#1 (COVID-19 or COVID or novel coronavirus 2019 or coronavirus disease 2019 or 2019-nCoV or SRAS-CoV-2) AND (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or ACEI or ARB or renin-angiotensin system inhibitor or renin-angiotensin system blocker or RAAS or hypertension or antihypertensive agent) (446)

Limiters - Date of Publication: 20200101-20200601; English Language
Expanders - Apply equivalent subjects
Search modes - Find all my search terms

Cochrane Library
#1 (COVID-19):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent):ti,ab,kw (28)
#2 (novel coronavirus 2019):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent):ti,ab,kw (4)
#3 (coronavirus disease 2019):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent):ti,ab,kw (10)
#4 (nCoV):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent):ti,ab,kw (2)
#5 (SRAS-CoV-2):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACEi OR ARBs OR renin-angiotensin system inhibitor OR renin-angiotensin system blocker OR RAAS inhibitors OR hypertension OR antihypertensive agent):ti,ab,kw (0)

2. Strength of the study

To the best of our knowledge, this is the first systematic review study to evaluate whether various individual the use of RAASi is associated with the increased risk of SARS-CoV-2 infection. Our findings represent the current best evidence to confirm the safety of the use of RAASi in the population as a whole, and yet caution the use of ARBs among a subpopulation of younger patients for its slightly but significantly higher SARS-CoV-2 infection rate. The strength of our meta-analysis lies in the large sample size and comprehensive data search across several continents. We adapted the GRADE approach to rate the certainty of evidence. Finally we identified and addressed a detailed body of published work from China, especially those in Chinese language from which much evidence emerged from the initial pandemic area.

3. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify	6

		additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Appendix
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7, Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7, Appendix
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7, Appendix

Section/topic	#	Checklist item	Reported on page #

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7, Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7, Appendix
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, 1s-Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, 8 Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11, Table2, s-Fig2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11, s-Table1, Fig,1,2,4 s-Fig5,6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-11, s-Fig3,4

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-11, Fig3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-17, Appendix
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

4. Summary of contextual factor data

There are three case-control studies, including Abajo et al. (2020) is a case-population study with 1139 cases and 11390 population control. And the users of RAAS inhibitors had an adjusted OR 0.94 (95% CI 0.77-1.15) for COVID-19 requiring hospital admission and no increased risk was noted either in the usage of ACEI (aOR 0.8, 0.62-1.00) or ARBs (aOR 1.10, 0.88-1.37). Mancia et al. (2020) is a population-based case-control study with 6272 cases with SARS-CoV-2 infection matching to 30759 Regional Health Service databases. The use of ACEi and ARBs did not associate with COVID-19 cases in ACEi (aOR 0.96, 0.87-1.07) and ARBs (aOR 0.95, 0.86-1.05) or patients with fatal course of COVID-19 in ACEi (aOR 0.91, 0.69-1.21) and ARBs (aOR 0.83, 0.63-1.10) after adjusting all the confounders. Huh et al. (2020) is also a case-control study using nationwide database with 65,149 subjects tested for COVID-19 and 5,172 patients (7.9%) diagnosed with COVID-19. In the analysis of medication usage, ARBs associated with a higher risk of COVID-19 after adjusting for comorbidities and other concomitant medications (aOR 1.13, 1.01–1.26; p=0.034), compared to ACEI usage, which is not significantly associated with COVID-19.

There are four cohort studies. Mehta et al. (2020) is a retrospective cohort study with 18472 patients tested for SARS-CoV-2 with 1735 cases tested positive. After overlap propensity score weighting, the usage of ACEI (OR 0.89, 0.72-1.10) and ARBs (OR 1.09, 0.87-1.37) in tested positive patients showed no association between ACEI/ARB usage and positive COVID-19 test results. Rentsch et al. (2020) is also a retrospective cohort study with 3789 patients receiving COVID-19 test and 585 cases with positive results. And the usage of ACEI/ARBs was not significantly associated with hospitalization (aOR 1.24, 0.79-1.95) and intensive care (aOR 1.69, 1.01-2.84) after adjusting confounders. Reynolds et al. (2020) is a population-based cohort study with 12594 patients tested for COVID-19 and 5894 with positive results (46.8%). In 4357 hypertensive patients, 2573 cases were tested positive. No substantial increase in likelihood of COVID-19 tested positive or in the risk of severe COVID-19 patients in association with antihypertensive, including ACEi and ARBs. Besides, Chodick et al. (2020) is a cross-section study with 1317 cases with positive SARS-CoV-2 and 13203 with negative results as the control group. And after adjusting all the confounders, including sex, age, hypertension, diabetes, BMI, and heart failure, either in ACEi (aOR 1.18, 0.87-1.61) or ARBs (aOR 1.29, 0.93-1.79) did not increase the risk of COVID-19.

From above references, the association between ACEi/ARBs exposure did not increase the risk of COVID-19. Of note, our study focused on patients tested positive COVID-19 results with the usage of RAASi information, and the corresponding negative controls as well, that is different from other study designs. However, there are several study limitations, including several potential unmeasured confounding interactions in the design of observational studies, the smaller numbers of patients in the sub-analysis groups, and the lack of clinical outcomes of these SARS-CoV-2 infected patients in each of the studies, that might provide enough information regarding the susceptibility and worse clinical outcomes of SARS-CoV-2 infection.

In conclusion, the usage of either ACEi, ARBs, or RAASi associated with the risk of positive SARS-COV-2 test, and further sub-analysis the data, the usage of ARBs compared to non-user, significantly increased the risk of SARS-CoV-2 infection in younger population. And our study raised attention of the contextual factors, such as age and the RAASi usage during the COVID-19 pandemic era.

5. PROSPERO protocol registration

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Use of renin-angiotensin-aldosterone system inhibitors and risks of COVID-19

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

25/05/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

05/07/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record. Yu-Shan Huang

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Huang

7. * Named contact email.

Give the electronic mail address of the named contact.

b101091021@gmail.com

8. Named contact address

Give the full postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+886-972651391

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

National Taiwan University Hospital

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. NOTE: email and country are now mandatory fields for each person.

Dr Chieh-Kai Chan. National Taiwan University Hospital Dr
Yu-Shan Huang. National Taiwan University Hospital Dr
Hung-Wei Liao. Jia-yi Clinic
Dr I-Jung Tsai. National Taiwan University Hospital Dr
Chiao-Yin Sun. Chang Gung Memorial Hospital
Professor Jeff S Chueh. Glickman Urological and Kidney Institute, Cleveland Clinic · Dr
Vin-Cent Wu. National Taiwan University Hospital

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

No funding sources or sponsors

Grant number(s)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

1. Does prior treatment with Renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), compared to subjects without RAAS inhibitors use, increase the risk of COVID-19?

2. Is there a different effect between ACEIs and ARBs on the susceptibility to COVID-19?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We systematically assessed the PubMed, Embase, medRXIV and Cochrane Library databases, with a start date of Jan 1 2020 and an end date of Jun 9, 2020, to identify relevant studies that met predetermined inclusion criteria.

The following search terms were used to identify relevant articles: (COVID-19 OR novel coronavirus 2019 OR coronavirus disease 2019 OR 2019-nCoV OR SRAS-CoV-2) AND (angiotensin-converting enzyme inhibitors OR angiotensin receptor blockers OR ACE INHIBITORS OR ARB OR renin-angiotensin system inhibitors OR renin-angiotensin system blockers OR RAAS) OR (hypertension).

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy

for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Coronavirus disease-2019 (COVID-19)

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: Patients who were tested for COVID-19

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Patients without the use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB).

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Non-randomised observational studies (cohort studies, case-control studies, and case series).

Studies reporting on outcomes comparing patients treated with an angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) versus patients not treated with ACE inhibitors or ARBs and their rates of confirmed COVID-19 infection.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Likelihood of a positive test result for SARS-CoV-2 infection in patients with or without prior treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB).

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Odds ratio (95% confidence intervals).

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Likelihood of a positive test result for SARS-CoV-2 infection in patients with or without prior treatment with RAAS inhibitors among different age groups and different countries

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Odds ratio (95% confidence intervals).

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The searched articles were first evaluated by two independent investigators at the title or abstract for inclusion. If there were disagreements, the comments from a third reviewer were sought. For potentially relevant searched articles, the full version was further retrieved and evaluated according to the selection criteria. Eligible studies were cohort or case-control studies reporting on the risk factors of COVID-19, including use of RSSA inhibitors, and the test results of SARS-CoV-2. When the results of a study were reported in more than one publication, the most informative and recent publication was included in the analysis. Articles that were duplicate publications, case reports, reviews, editorials, letters, and commentaries were excluded.

The two investigators who performed the literature search also independently extracted the data from the included studies using a standardized data spreadsheet. Discrepancies were resolved through consensus or referral to a third reviewer. The following variables were extracted: author, journal, publication year, study design, geographical location, participants' details (number, study population, age, and gender, comorbidities including hypertension, diabetes, and cardiovascular disease), use of antihypertensive drugs such as ACEIs, ARBs, calcium-channel blockers, beta-blockers, diuretics, outcomes (diagnosis of COVID-19). Study authors were not contacted for additional information.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

The quality of the included studies was assessed independently by two investigators using the Newcastle–Ottawa Quality Assessment Scale (NOS) scoring system.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

Data will be synthesized if studies report the outcomes which compared the risk of SARS-CoV-2 infection between patients using angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) or both versus patients who were not using any ACE inhibitors or ARBs.

When more than one study is available for each outcome, we will pool these together for quantitative analysis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of all outcomes were calculated using the random effects model. Heterogeneity was estimated from the inverse-variance random-effect model.

Statistical heterogeneity among studies was assessed by the$\chi 2$ test (p 0.05 was defined as indicating significant heterogeneity) and calculation of I^2.

Because between-study heterogeneity can be misleadingly large when quantified by I^2 during meta-analysis of observational studies, we used GRADE guidance to assess between-study heterogeneity. We analyzed the effect of RAAS inhibitors on the risk of COVID-19 by random-effects univariate meta-regressions, using restricted maximum likelihood, and we present mean effects and 95% CIs. A funnel plot and the Egger test were used to assess the publication bias. In order to explore potential differences and assess heterogeneity between the data sets, we further did univariate and multivariate meta-analyses to examine the effect on the basic characteristics of the SARS-COV-2 infection by random-effects models, and we present mean effects and 95% CIs.

The statistical analyses will be performed using STATA version 13, Review Manager 5.3. and Comprehensive Meta-Analysis Software (CMA).

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

The effect of RAAS inhibitors may not be the same among different classes of medication or age groups. Therefore, a subgroup analysis was performed for patients 60 years or ≥60 years and ACEI or ARB. Meta- regression was the analytic approach.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

No

Meta-analysis

Yes

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health No

Complementary therapies
No

COVID-19
Yes

Crime and justice No

Dental
No

Digestive system No

Ear, nose and throat No

Education
No

Endocrine and metabolic disorders No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity No

Infections and infestations Yes

International development
No

Mental health and behavioural conditions No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health) No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error. English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Taiwan

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one Give

the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

We had revised the section of "Strategy for data synthesis." The detailed statistical methods for analysis were provided.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the link to the published review.

6. The GRADE results

Author(s): Chieh-Kai Chan, Yu-Shan Huang, Hung-Wei Liao, I-Jung Tsai, Chiao-Yin Sun, Heng-Chih Pan, Jeff S Chueh, Jann-Tay Wang, Vin-Cent Wu, Tzong-Shinn Chu
Question: ACEi compared to no ACEi for SARS-CoV-2 infection
Setting: Any
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEI	no ACEI	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV-2 infection												
7	observational studies	not serious	not serious	not serious	not serious	none	2756/14921 (18.5%)	19358/149163 (13.0%)	**aOR ranged from** 0.86 to 1.05	not estimable	⨁⨁◯◯ LOW	CRITICAL
Severity or mortality of SARS-CoV-2 infection												
4	observational studies	not serious	serious [a]	not serious	not serious	none	476/2485 (19.2%)	1807/12555 (14.4%)	**aOR ranged from** 0.80 to 1.26	not estimable	⨁◯◯◯ VERY LOW	CRITICAL

ACEi: angiotensin-converting enzyme inhibitor; aOR: adjust odds ratio; CI: Confidence interval
Explanations
a. There was a high I2 value

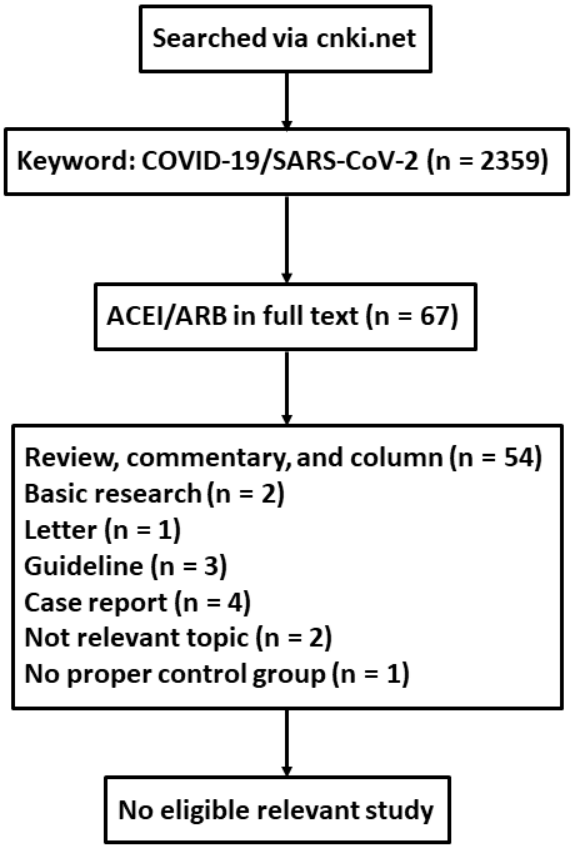
Question: ARBs compared to no ARBs for SARS-CoV-2 infection
Setting: Any
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	no ARB	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV-2 infection												
7	observational studies	not serious	not serious	not serious	not serious	none	3352/22685 (14.8%)	18762/141399 (13.3%)	**aOR ranged from** 0.97 to 1.14	not estimable	⨁⨁◯◯ LOW	CRITICAL
Severity or mortality SARS-CoV-2 infection												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	no ARB	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	not serious	not serious	not serious	not serious	none	485/2507 (19.3%)	1842/12533 (14.7%)	**aOR ranged from** 0.83 to 1.18	not estimable	⨁⨁◯◯ LOW	CRITICAL

ARBs: angiotensin II type 1 receptor antagonists; aOR: adjust odds ratio; CI: Confidence interval

7. Flow chart showing Search strategy for studies in China.



8. Supplemental Tables and Figures

Table S1. Newcastle-Ottawa Scale Quality Assessment of included studies

	Selection				Comparability		Exposure			
First author / Year	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability: Age and Sex	Comparability: Additional Factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response Rate	Total
Abajo/2020	*	*	-	*	*	*	*	-	*	7
Chodick/2020	*	*	*	*	*	*	*	*	*	9
Huh/2020	*	*	*	-	*	*	*	*	*	8
Mancia/2020	*	*	*	*	*	*	*	*	*	9
Mehta/2020	*	*	*	*	*	*	*	*	*	9
Rentsch/2020	*	*	*	*	*	*	*	*	*	9
Renolds/2020	*	*	*	*	*	*	*	*	*	9

Table S2. Univariate meta-regression analysis of the possible effect modification of each characteristic

	Number of	ACEi users vs non-ACEi users		ARBs users vs non-ARBs users	
Covariate	studies	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Mean or median age	6	-0.006 (-0.016 to 0.004)	0.221	-0.006 (-0.012 to -0.0002)	**0.042**
Proportion of men	6	-0.002 (-0.014 to 0.010)	0.764	-0.004 (-0.013 to 0.005)	0.376
Proportion of hypertension	6	-0.006 (-0.015 to 0.002)	0.143	-0.007 (-0.013 to 0.001)	**0.028**
Proportion of diabetes	6	-0.003 (-0.021 to 0.016)	0.784	0.007 (-0.003 to 0.016)	0.183
Proportion of heart failure	5	-0.015 (-0.046 to 0.015)	0.324	0.001 (-0.035 to 0.036)	0.970
Proportion of kidney disease	5	0.019 (-0.033 to 0.070)	0.483	0.015 (-0.009 to 0.039)	0.211

Abbreviations: ACEi, angiotensin- converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval.

Figure S1. Flow chart showing the meta-analysis studies selection.

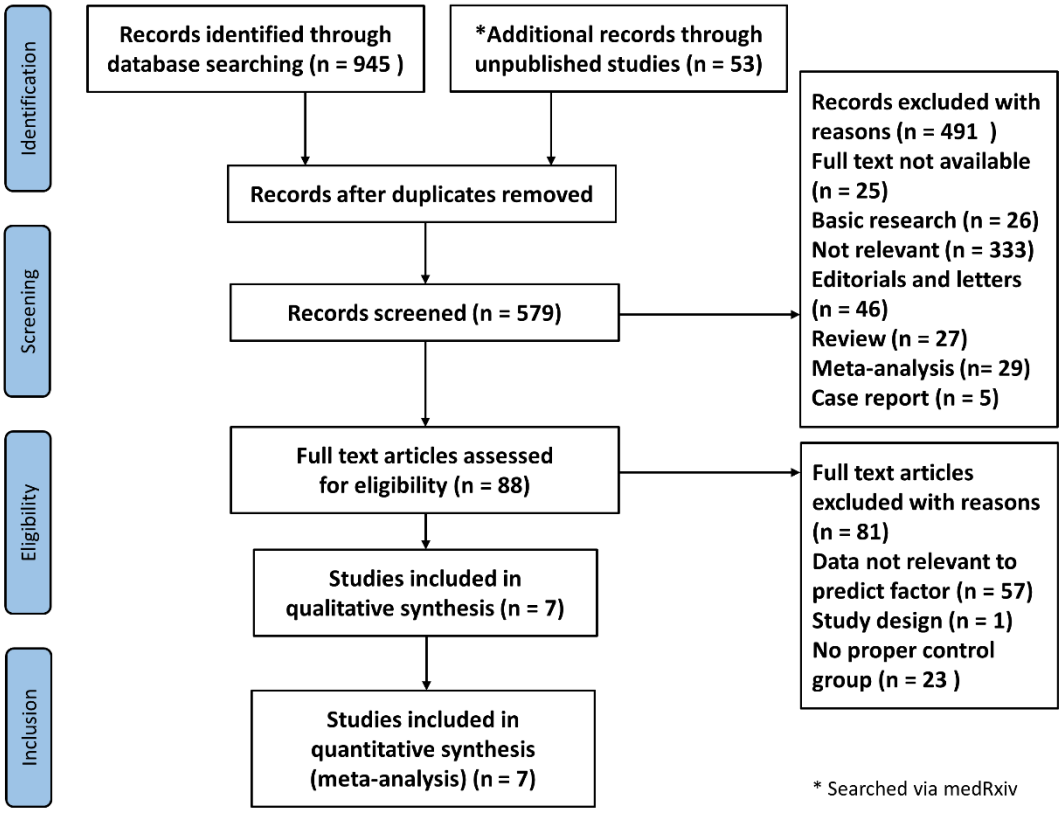


Figure S2. The forest plot showing the association of ACEi use or ARBs use and the risk of SARS-CoV-2 infection by pooling the crude odds ratios.

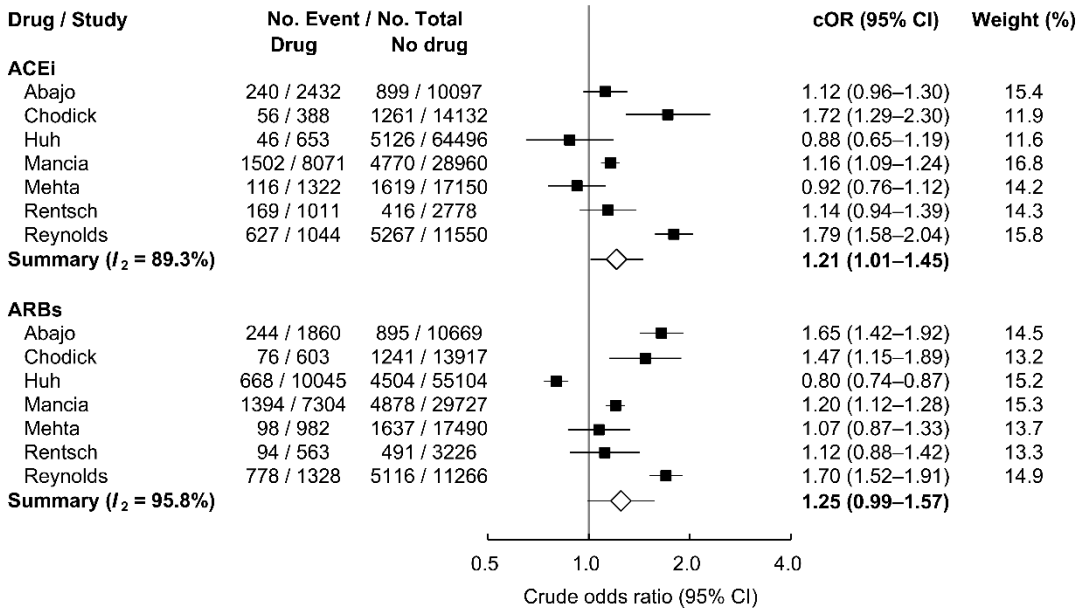


Figure S3. The funnel plot showing the visual check for publication bias of the effect of ACEi use on the risk of SARS-CoV-2 infection by pooling the adjusted odds ratios.

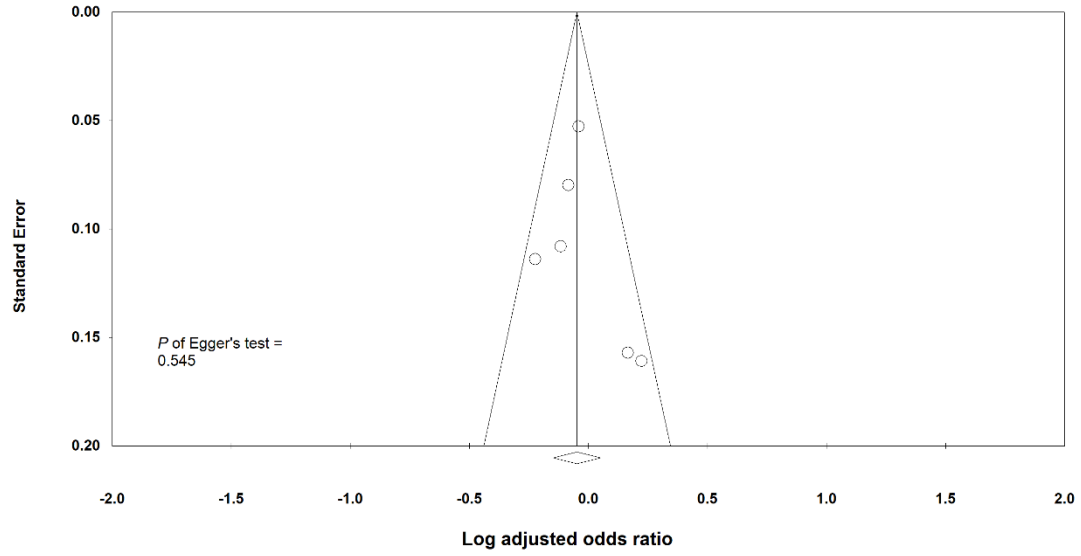


Figure S4. The funnel plot showing the visual check for publication bias of the effect of ARBs use on the risk of SARS-CoV-2 infection by pooling the adjusted odds ratios.

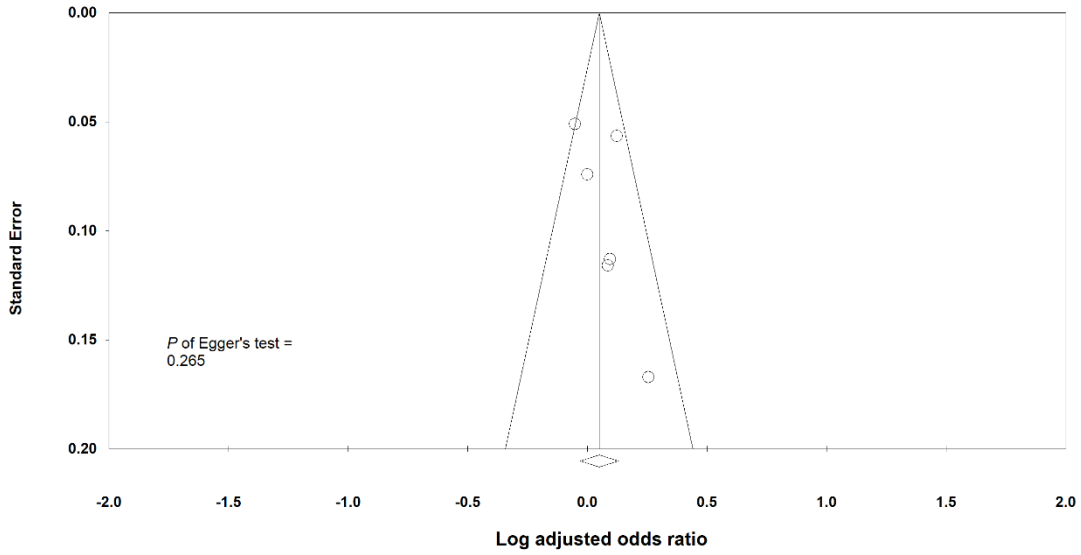
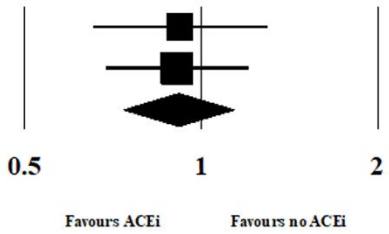


Figure S5. The forest plot showing the association of ACEi use and the risk of severity and mortality of SARS-CoV-2 infection stratified by the mean or median age of 60 years. (S5a: >60 y/o subgroup; S5b: <60y/o subgroup)

a

Study name	Adjust odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Abajo	0.920	0.653	1.296	-0.477	0.633
Mancia	0.910	0.687	1.205	-0.658	0.510
Total	0.914	0.736	1.136	-0.811	0.417



b

Study name	Adjust odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Mehta	1.770	1.071	2.924	2.229	0.026
Reynolds	0.900	0.713	1.135	-0.889	0.374
Total	1.215	0.629	2.347	0.579	0.562

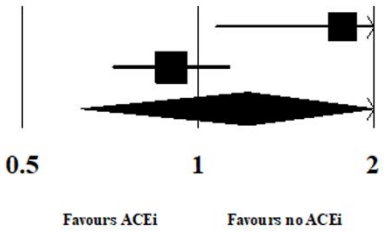
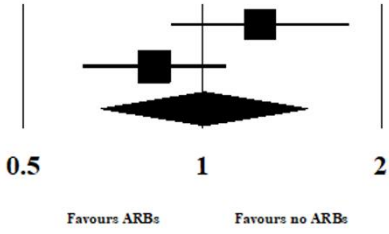


Figure S6. The forest plot showing the association of ARBs use and the risk of severity and mortality of SARS-CoV-2 infection stratified by the mean or median age of 60 years. (S6a: >60 y/o subgroup; S6b: <60y/o subgroup)

a

Study name	Adjust odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Abajo	1.250	0.886	1.763	1.272	0.203
Mancia	0.830	0.628	1.097	-1.310	0.190
Total	1.006	0.674	1.501	0.027	0.978



b

Study name	Adjust odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Mehta	1.160	0.668	2.014	0.527	0.598
Reynolds	0.960	0.766	1.203	-0.354	0.723
Total	0.986	0.800	1.216	-0.128	0.898